(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2002 (24.01.2002)

PCT

(10) International Publication Number
WO 02/06280 A2

(51) International Patent Classification[7]: C07D 417/14, 417/12, 401/12, 209/16, 403/12, 413/12, A61K 31/425, 31/33

(21) International Application Number: PCT/US01/22077

(22) International Filing Date: 13 July 2001 (13.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/218,051 13 July 2000 (13.07.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/06280 A2

(54) Title: INHIBITORS OF FACTOR Xa

(57) Abstract: Novel compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful in vitro or in vivo for preventing or treating coagulation disorders.

INHIBITORS OF FACTOR Xa

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel oligopeptide-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in

the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure," J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and

Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency," Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants," Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al., "Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors," Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene, -C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds are needed which selectively or preferentially bind to Factor Xa. Compounds with a higher affinity for binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability or other pharmacologically desirable properties. This invention answers such a need.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention provides compounds comprising a substituted primary chain structure having at least two to four peptide bonds included in the chain and may have at least one additional peptide bond structure included in a side chain attached to primary chain structure. These compounds are potent and selective inhibitors of factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents. Particular embodiments of the compounds of the present invention are set forth below as preferred embodiments and include all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes

pharmaceutical compositions comprising a pharmaceutically or therapeutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising administering the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by disorders of the blood coagulation process or thrombosis in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified, alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure" and "C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each

intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic, and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings, when present in the monocyclic, bicyclic or tricyclic ring structure, may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure provided that such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include

phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which may be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise, the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom; for example, bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means

that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents provided that such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than one, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that one O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, include: acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein, the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl," and the like, refer to aliphatic carbon radicals having at least one hydrogen atom substituted by a Cl, Br, F or I atom, including mixtures of different halo atoms. For example, trihaloalkyl includes trifluoromethyl and the like as preferred radicals.

The term "methylene" refers to $-CH_2-$.

In addition, the following abbreviations are used in this application: "Boc" refers to t-butoxycarbonyl; "BOP" refers to benzotriazol-1-yloxy-tris-(dimethylamino) phosphonium hexafluorophosphate; "DIEA" refers to diisopropylethylamine; "DMF" refers to N,N-dimethylformamide; "Et_2O" refers to diethyl ether; "EtOAc" refers to ethyl acetate; "HF" refers to hydrogen fluoride; "ICH_2COOEt" refers to ethyl iodoacetate; "$LiN(TMS)_2$" refers to lithium bis-trimethyl silyl amide; "MeSEt" refers to methyl ethyl sulfide; "TFA" refers to trifluoroacetic acid; "THF" refers to tetrahydrofuran; "TMSI" refers to trimethyl silyl iodide; and "Tos" refers to *p*-toluenesulfonyl.

For organic compounds of this invention, carbon atoms bonded to four non-identical substituents are considered asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products

resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques as well as by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S), both of which are within the scope of the present invention. In the processes described above, the final products may, in some cases, contain a small amount of diastereomeric or enantiomeric side-products; however, these side-products do not affect the therapeutic or diagnostic application of the final products.

In all of the peptides of the invention, one or more amide linkages (-CO-NH-) may optionally be replaced with another linkage which is an isostere such as $-CH_2NH-$, $-CH_2S-$, $-CH_2-O-$, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, and $-CH_2SO_2-$. This replacement can be made by methods known in the art. The following references describe preparation of peptide analogs which include these alternative-linking moieties: Spatola, "Peptide Backbone Modifications" (general review) Vega Data, Vol. 1, Issue 3, (March 1983); Spatola, "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," (general review) B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983); Morley, Trends Pharm. Sci. (general review) pp. 463-468 (1980); Hudson, *et al.*, Int. J. Pept. Prot. Res. 14:177-185 (1979) ($-CH_2NH-$, $-CH_2CH_2-$); Spatola, *et al.*, Life Sci. 38:1243-1249 (1986) ($-CH_2-S$); Hann, J. Chem. Soc. Perkin Trans. I pp.307-314 (1982) (-CH=CH-, cis and trans); Almquist, *et al.*, J. Med. Chem. 23:1392-1398 (1980) ($-COCH_2-$); Jennings-White, *et al.*, Tetrahedron Lett. 23:2533 ($-COCH_2-$) (1982); Szelke, *et al.*, European Application EP 45665; CA:97:39405 (1982) ($-CH(OH)CH_2-$); Holladay, *et al.*, Tetrahedron Lett 24:4401-4404 (1983) ($-CH(OH)CH_2-$); and Hruby, Life Sci. 31:189-199 (1982) ($-CH_2-S-$).

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free-base and salt form. In practice, the use of the salt form is equivalent to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

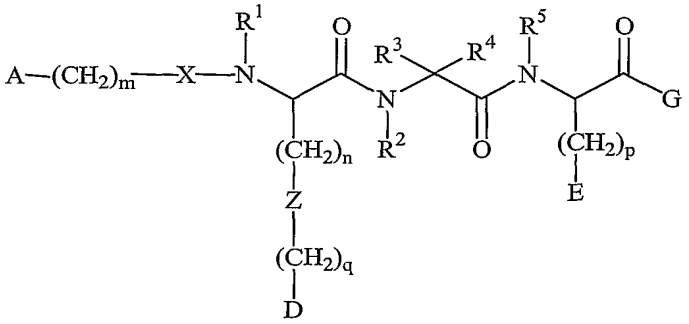
"Pharmaceutically acceptable base addition salts" include those salts derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that is often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, and any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

For the organic compounds of this invention, carbon atoms bonded to four non-identical substituents are considered asymmetric. Accordingly, these compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S), both of which are within the scope of the present invention.

Preferred Embodiments

An embodiment of the invention provides a compound of the formula (I):



(I)

wherein:

R^1 and R^5 are independently H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

R^2 is H, C_{1-6} alkyl, C_{0-4} alkylC_{3-8}cycloalkyl, C_{0-4} alkylaryl, C_{0-4} alkylC_{5-10}heterocycle or together with R^3 or R^4 forms a 5-8 membered ring;

R^3 and R^4 are independently H, C_{1-6} alkyl, C_{0-4} alkylC_{3-8}cycloalkyl, C_{0-4} alkylaryl, C_{0-4} alkylC_{5-10}heterocycle, or R^3 and R^4 together form a 3-8 membered ring;

A is H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, substituted or unsubstituted aryl, or a substituted or unsubstituted 5-10 membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

m is an integer from 0-4;

X is a direct link, -C(=O)-, $-SO_2-$, -O-C(=O)-, $-NR^6-SO_2-$, $-C(=O)-NR^6-$, -S-,
-S(O)-, or $-NR^6-C(O)-$,

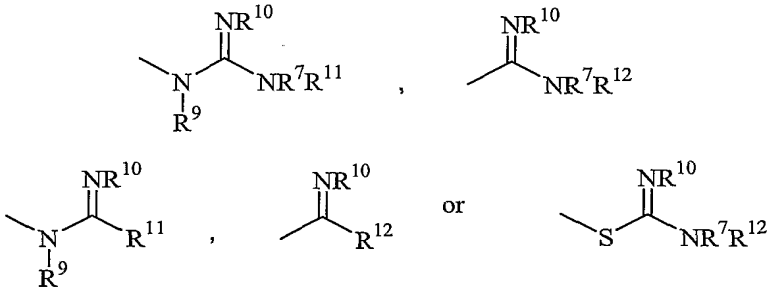
where R^6 is H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

n is an integer from 0-4;

Z is a direct link, C_{1-6} alkylene, C_{3-8} cycloalkylene, divalent aryl, a substituted or unsubstituted divalent 5-10 membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, -S-, -S(O)-, $-SO_2-$, -O-, -C(O)-O-, -C(O)-, -O-C(O)-, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-C(O)-NR^6-$, or $-NR^6-C(O)-$, where R^6 is H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

q is an integer from 0-2;

D is H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{5-10} heterocycloalkyl, aryl, C_{5-10} heteroaryl, NR^7R^8,



where R^7, R^8, R^9, R^{10} are independently H, -OH, $-C_{1-6}$ alkyl, aryl, or C_{1-4} alkylaryl;

R^{11} is H, C_{1-6} alkyl, aryl, C_{1-4} alkylaryl, or together with R^9 or R^{10} forms a 5-6 membered ring; and

R^{12} is H, C_{1-6} alkyl, aryl, C_{1-4} alkylaryl, or together with R^{10} forms a 5-6 membered ring;

or alternatively, R^7 and R^{12}, together with the nitrogen atom to which they are attached, can collectively form a 5-10 membered aromatic or nonaromatic heterocyclic ring system containing an additional 0-3 heteroatoms selected from the group consisting of N, O, S, -S(O)- and -SO_2-, wherein the aromatic or nonaromatic heterocyclic ring system may be substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and C_{0-4} alkylC_{5-10}heterocycle;

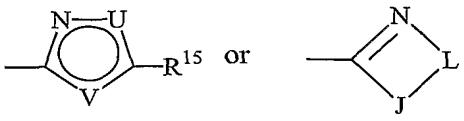
p is an integer from 0-4;

E is

(a) a cycloalkyl, aryl and C_{0-6} alkylaryl, wherein each of the cycloalkyl, or aryl portions may be unsubstituted or substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and C_{0-4} alkylC_{5-10}heterocycle; or

(b) a substituted or unsubstituted five to ten membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, wherein the aromatic or nonaromatic heterocyclic ring system can be substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and C_{0-4} alkylC_{5-10}heterocycle;

G is H, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-CF_3$, $-CF_2CF_3$ or a group having the formula:



wherein:

R^{13} and R^{14} are independently H, C_{1-6} alkyl, aryl or C_{1-4} alkylaryl;

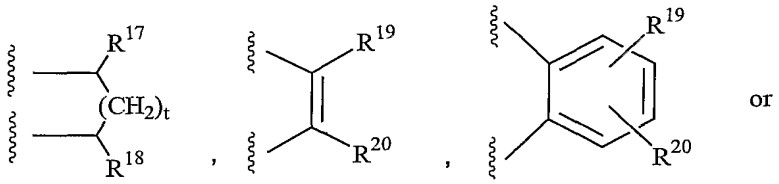
U is -O-, -S-, -N- or -NH-;

V is -O-, -S-, -N- or -NH-, with the proviso that at least one of U or V is -N-or -NH-;

R^{15} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{0-6} alkylaryl, C_{2-6} alkenylaryl, C_{0-6} alkylheterocycle,
C_{2-6} alkenylheterocycle, $-CF_3$ or $-CF_2CF_3$;

J is -S-, -S(O)-, $-SO_2$-, -O-, or $-NR_{16}$, where R^{16} is H, C_{1-6} alkyl or benzyl; and

L is:



a C_6-C_{10} aromatic or nonaromatic heterocyclic ring system substituted by R^{19} and R^{20} and containing 1-4 heteroatoms selected from N, S, and O;

t is an integer from 0-2;

R^{17} and R^{18} are independently H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, $-COOR^{21}$, $-C(O)NR^{21}R^{22}$,
-CN or $-CF_3$; and

R^{19} and R^{20} are independently H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen,
$-NO_2$, $-NR^{21}R^{22}$,$-NR^{21}C(O)R^{22}$, $-OR^{21}$, $-OC(O)R^{21}$, $-C(O)OR^{21}$, $-C(O)NR^{21}R^{22}$, $-CN$, $-CF_3$,
$-SO_2NR^{21}R^{22}$ or C_{1-6}alkyl-OR^{21}; and

R^{21} and R^{22} are independently H, C_{1-6}alkyl, aryl, or C_{1-3}alkylaryl,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Preferred are such compounds of formula (I) wherein m is an integer from 0-2; n is an integer from 1-3; q is an integer from 0-1; and p is an integer from 1-3 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

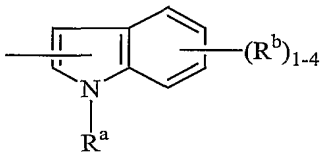
In another embodiment the present invention provides a compound according to formula (I), wherein E is a substituted or unsubstituted heterocyclic ring system, wherein the heterocyclic ring system is a member selected from the group consisting of:

acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl,

pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, and isatinoyl,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Particularly preferred compounds according to formula (I) are compounds wherein E is the heterocyclic ring system having the formula:



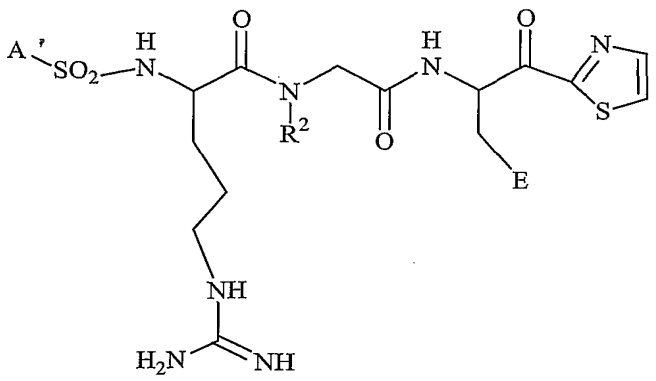
wherein

R^a is a member selected from the group consisting of H, trihaloalkyl, -O, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{0-4}$ alkylC_{3-8}cycloalkyl, $-C_{0-4}$ alkylaryl and $-C_{0-4}$ alkylC_{5-10}heterocycle;

each R^b is independently a member selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, $-C_{1-6}$ alkyl, -SH, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{0-4}$ alkylC_{3-8}cycloalkyl, $-C_{0-4}$ alkylaryl and $-C_{0-4}$ alkylC_{5-10}heterocycle,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another embodiment of the present invention is a compound according to formula (Ia) as follows:



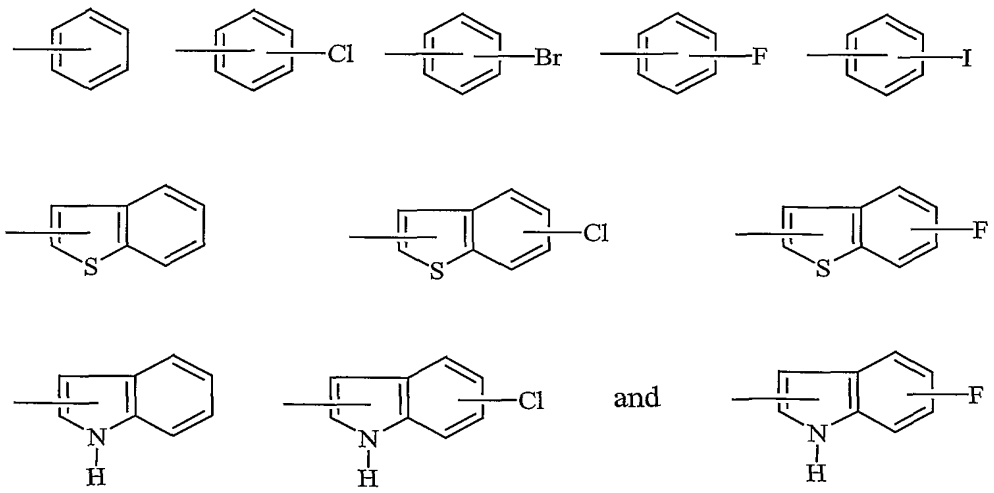
(Ia)

wherein:

A is a member selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, -phenyl, and $-CH_2$-phenyl;

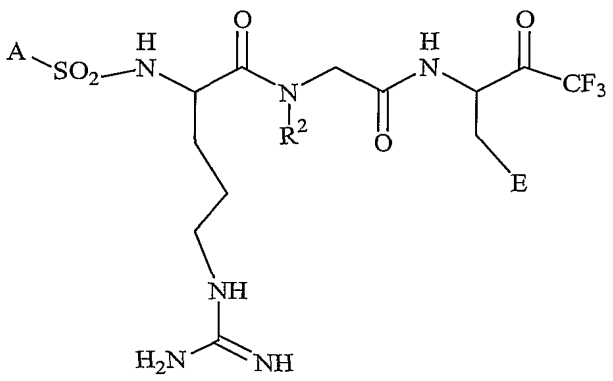
R^2 is a member selected from the group consisting of H, $-CH_3$, and -phenyl; and

E is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another embodiment of the invention provides a compound according to formula (Ib), as follows:



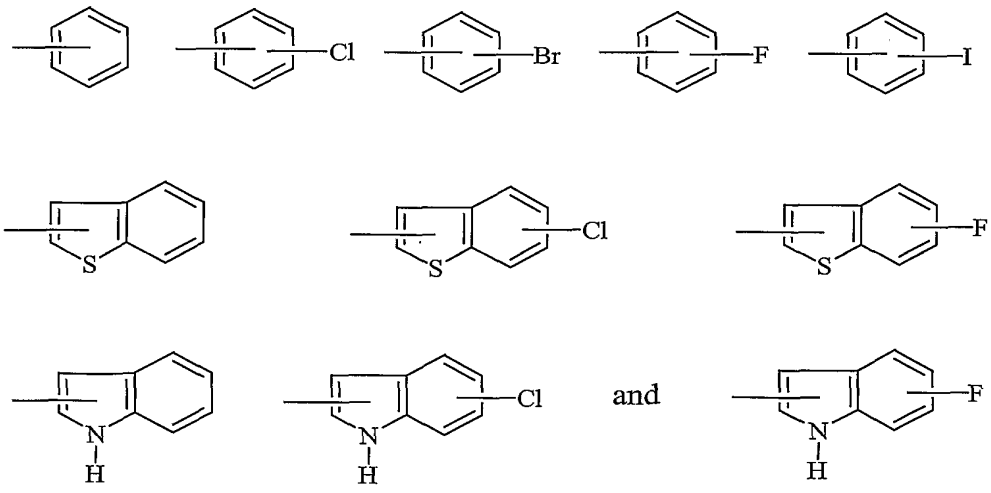
(Ib)

wherein:

A is a member selected from the group consisting of -CH_3, -CH_2-CH_3, -phenyl, and -CH_2-phenyl;

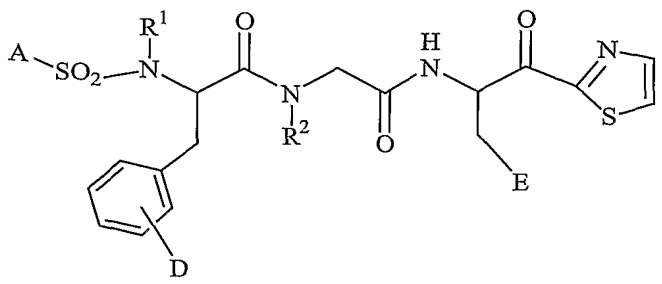
R^2 is a member selected from the group consisting of H, -CH_3, and -phenyl; and

E is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a further embodiment, the present invention provides a compound of formula (Ic), as follows:



(Ic)

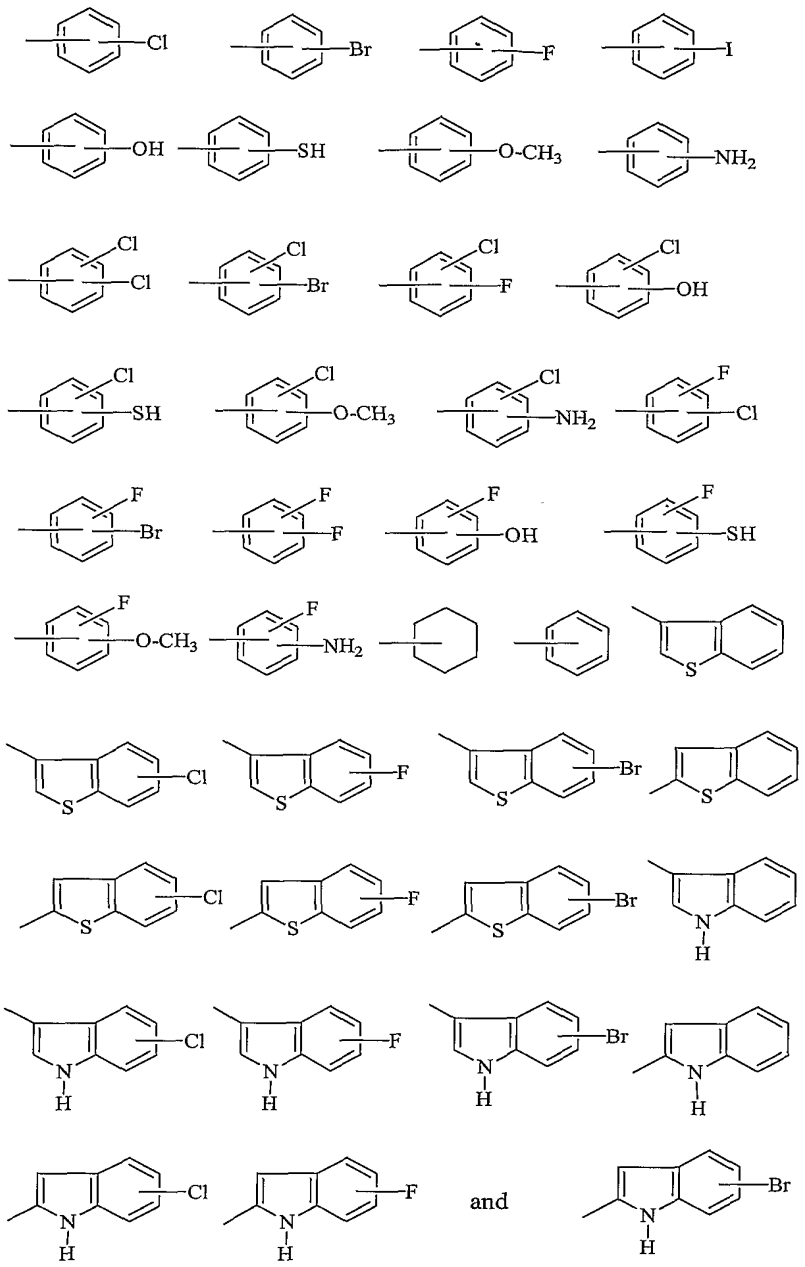
wherein:

A is a member selected from the group consisting of $-CH_3$, $-CH_2-CH_3$ and $-CH_2$-phenyl;

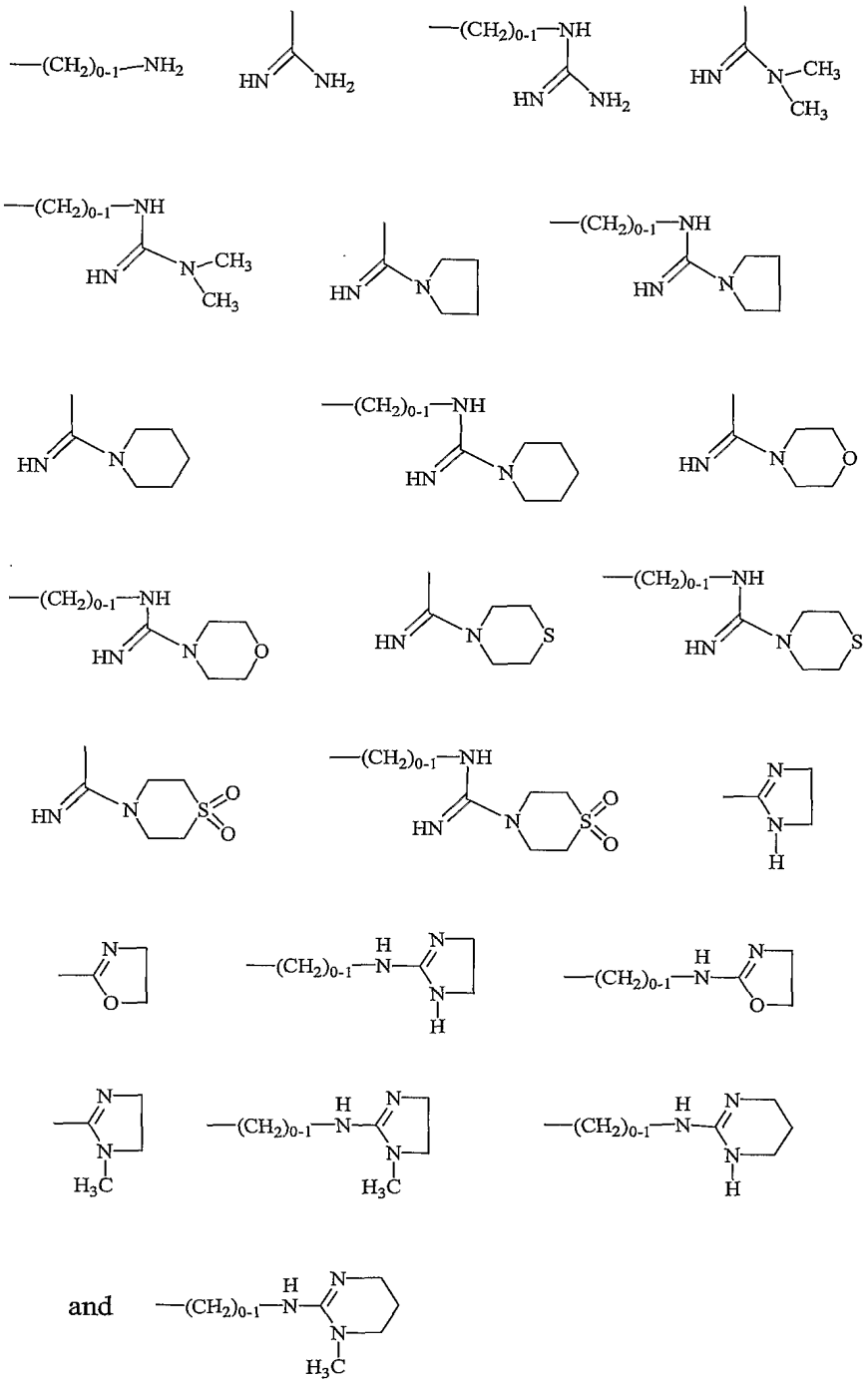
R^1 is a member selected from the group consisting of H, $-CH_3$, and $-CH_2$-phenyl; and

R^2 is a member selected from the group consisting of H, $-CH_3$, and -phenyl; and

E is a member selected from the group consisting of:

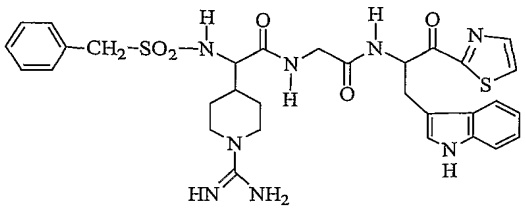


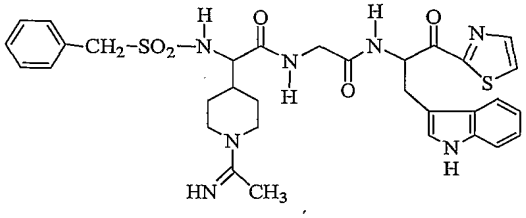
D is a member selected from the group consisting of:

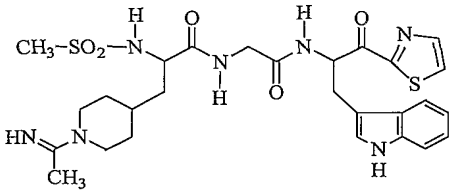


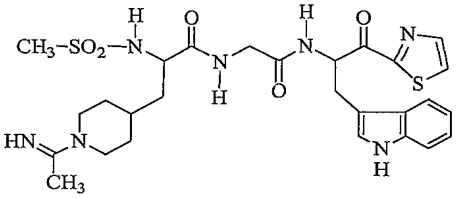
and all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrugs thereof.

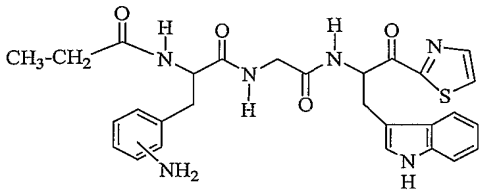
In another embodiment the present invention is a compound which is a member selected from the group consisting of:

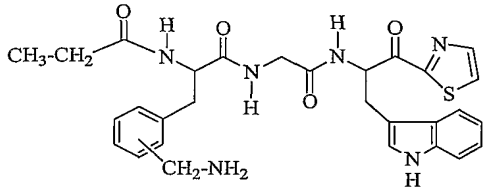


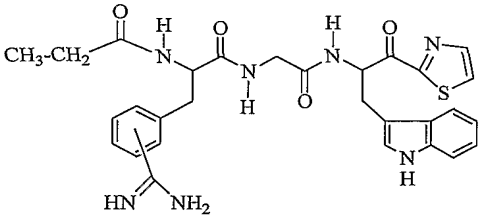


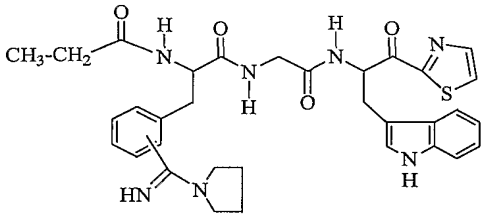












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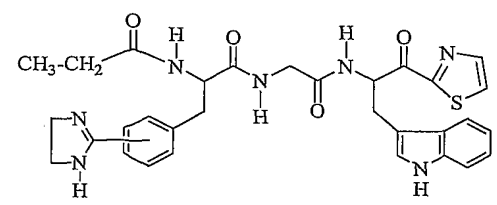
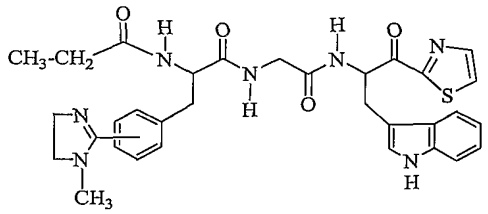
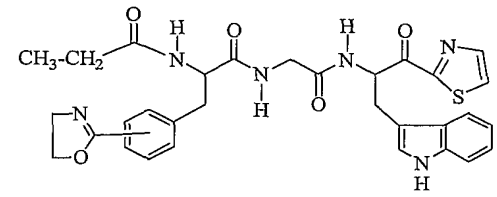
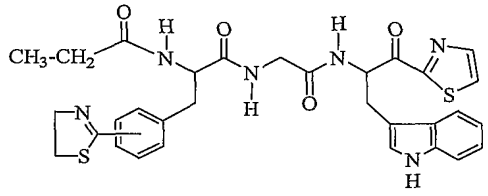
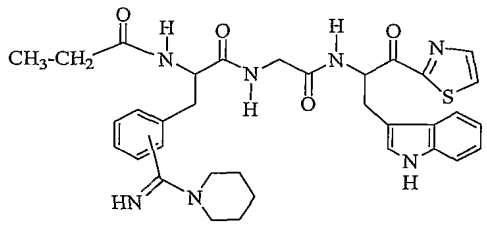
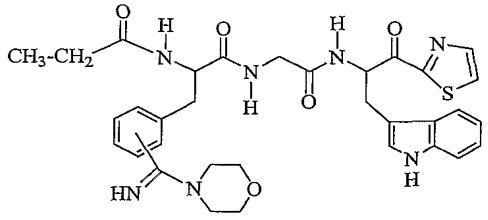


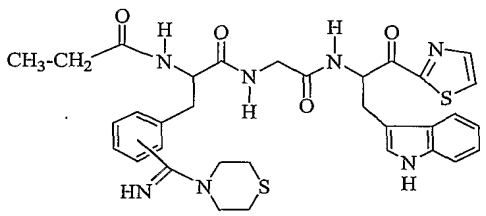


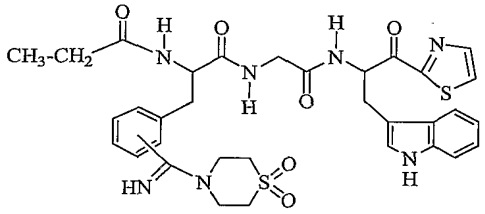




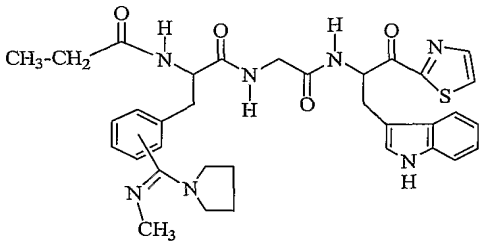






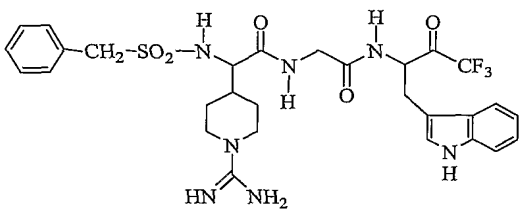


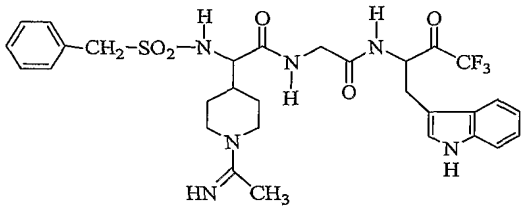
and

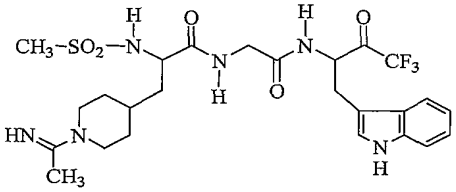


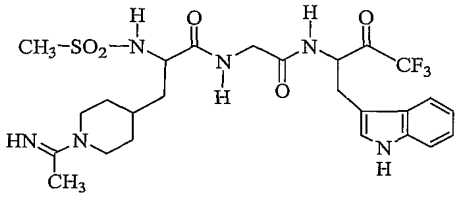
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

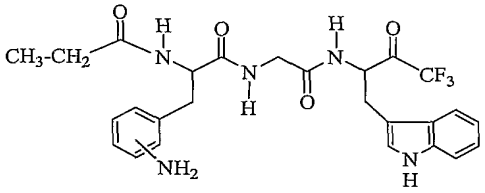
In another embodiment the present invention is a compound which is a member selected from the group consisting of:

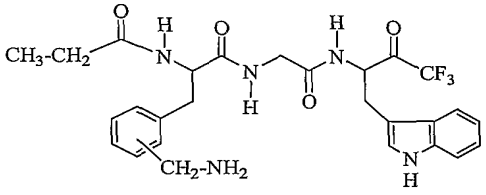


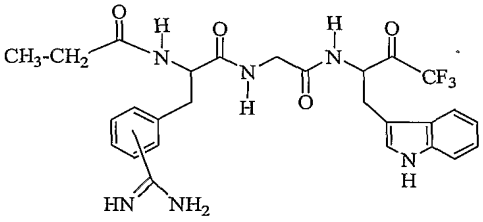


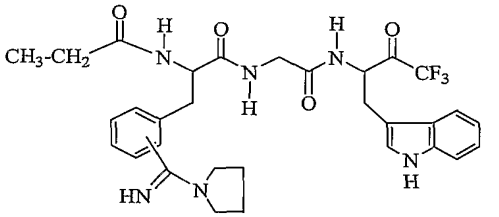












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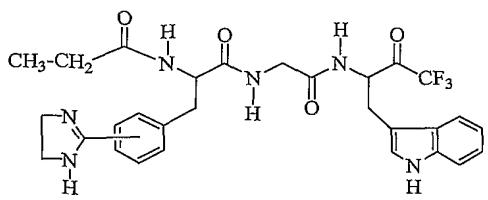
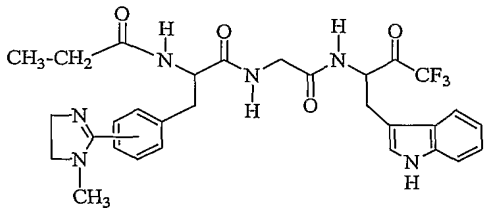
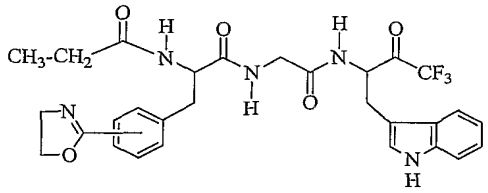
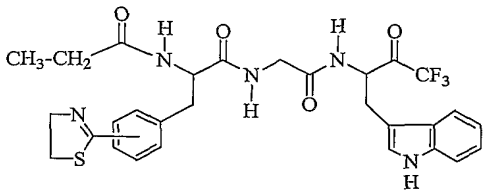
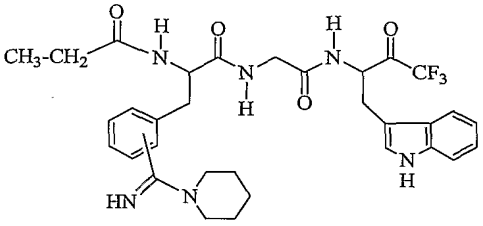
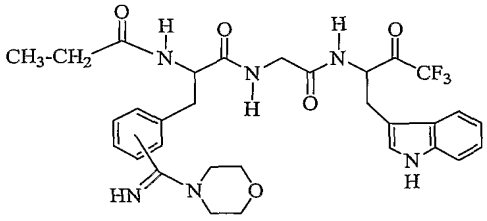


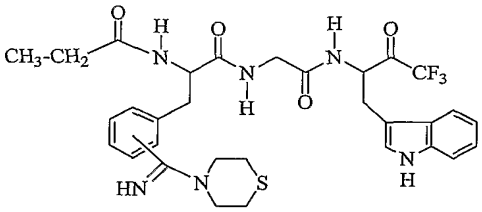


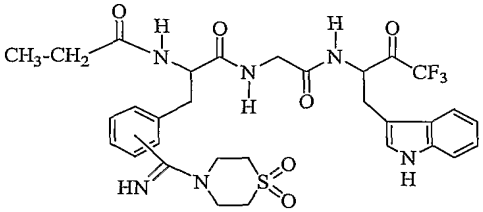




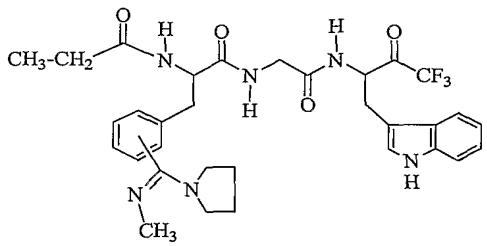






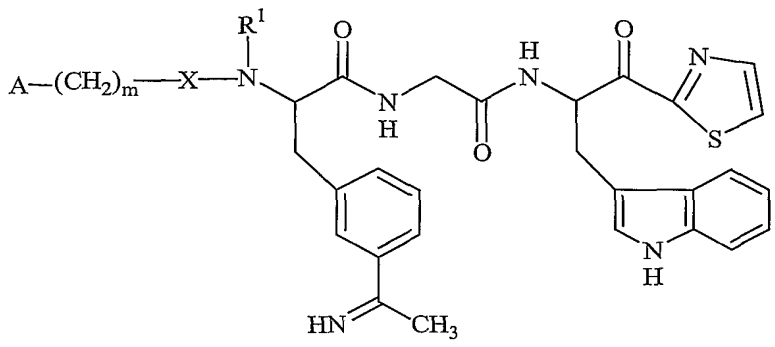


and



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment the present invention provides a compound according to formula (II) as follows:

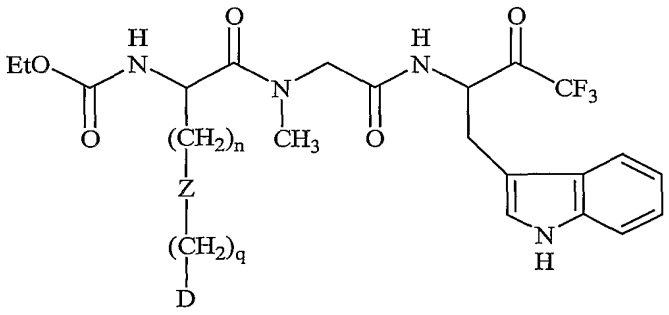


(II)

wherein A, m, X, and R^1 are each as described above for formula (I),

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In still another embodiment, the present invention provides a compound having the formula (III) as follows:

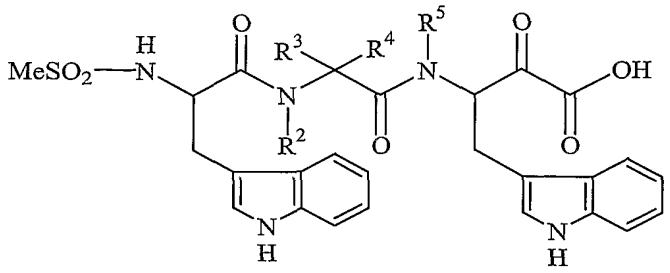


(III)

wherein n, Z, q, and D are each as described above for formula (I),

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment, the present invention provides a compound having the formula (IV) as follows:

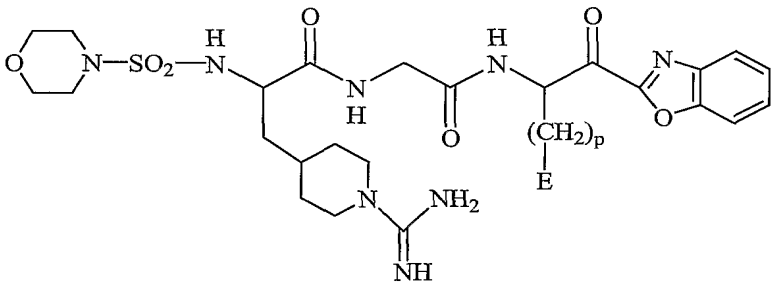


(IV)

wherein R^2, R^3, R^4, and R^5 are each as described above for formula (I),

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another embodiment of the present invention provides a compound of formula (V) as follows:

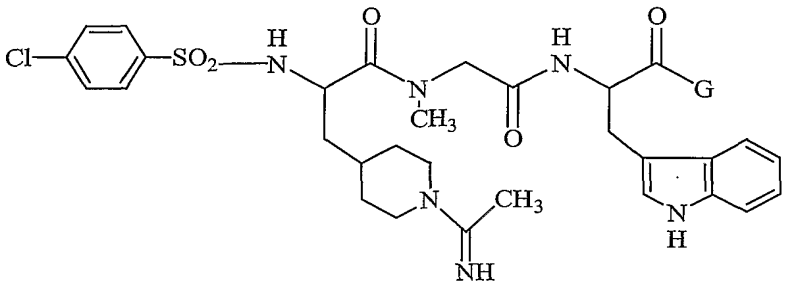


(V)

wherein E and p are each as described above for formula (I),

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a further embodiment, the present invention provides a compound of formula (VI) as follows:

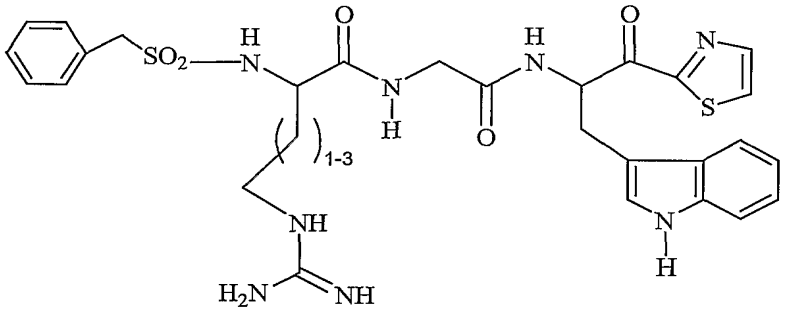


(VI)

wherein G is as described above for formula (I),

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In yet another embodiment, the present invention provides a compound according to formula VII, as follows:



(VII)

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to those of skill in the art, such as, for example, esters prepared by reacting the parent acids with a suitable alcohol, or amides prepared by reacting the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation, such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism, or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and

prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be

utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as

polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug

carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably in the range of about 0.5 to 50 mg/kg and more preferably in

the range of about 1 to 20 mg/kg on a regimen in a single daily dose or 2 to 4 daily doses (divided proportionally) and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of the free acid or base form or pharmaceutically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, it may also contain, in addition to the above materials, liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by standard organic chemical synthetic methods as described and referenced in standard textbooks. These methods are well known in the art. See, e.g., Morrison and Boyd, "Organic Chemistry," Allyn and Bacon, Inc., Boston, 1959, et seq.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

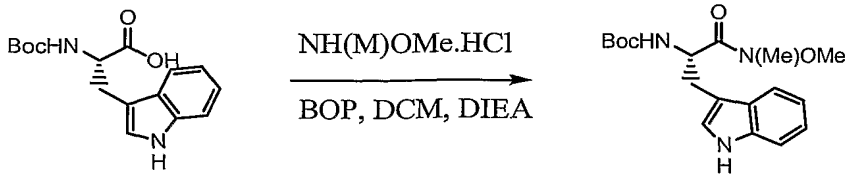
Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the substituents are optionally protected by blocking groups to prevent cross reaction during coupling procedures. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology," Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

A non-limiting exemplary synthesis scheme is outlined directly below, and specific steps may vary depending upon the specific substituents as described in the above descriptions of the compounds. Such variations on the general reaction scheme will be readily apparent to those of ordinary skill in the art in view of the above disclosure and the general reaction scheme set forth below. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods known to those of skill in art.

Experimental Procedures:

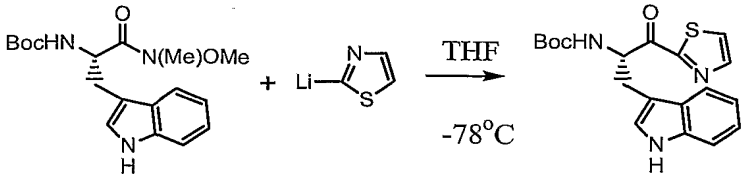
Step 1.



To a solution of Boc-Trp-OH (1.3 g), NH(Me)OMe.HCl (0.45 g) and 1.5 mL of DIEA in 60 mL of DCM at 0 °C was added BOP (1.7 g) and the mixture was stirred for 3 hr. Solvent was removed and residue was dissolved in 50 mL of EtOAc, washed with saturated $NaHCO_3$, saturated NaCl and 1 N HCl, and dried

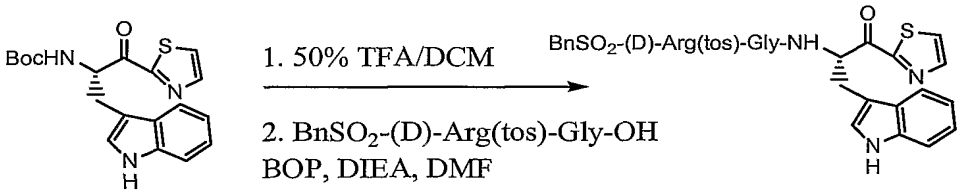
with Mg_2SO_4. After evaporation of the solvent, a solid residue was obtained (1.5 g).

Step 2.



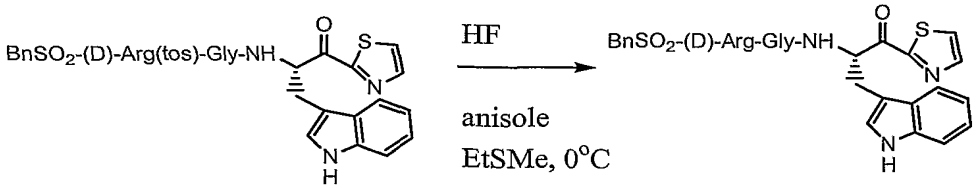
To a solution of Boc-Trp-N(Me)OMe (0.83 g) in THF was added lithoithiazole (10 mmol) at –78 °C and stirred for 2 hr. The mixture was stopped with addition of 20 mL of 1 N HCl. After work up, 1 gram of Boc-Trp-Thiazole was obtained.

Step 3.



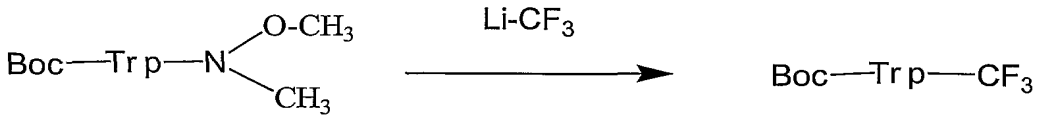
50 mg of Boc-Trp-thiazole was dissolved in 5 ml of DCM and treated with 5 ml of TFA. The solution was stirred for 1 hr. After the solvent was removed, the residue was coupled with $BnSO_2$-(D)-Arg(tos)-Gly-OH with Bop as a coupling reagent. The $BnSO_2$-(D)-Arg(tos)-Gly-Trp-thiazole was obtained after HPLC purification.

Step 4.



50 mg of $BnSO_2$-(D)-Arg(tos)-Gly-Trp-thiazole was treated with 2 ml of HF in the presence of anisole and EtSMe at 0°C for 30 min. After HPLC purification, the desired $BnSO_2$-(D)-Arg-Gly-Trp-Thiaozle (MS: M+H = 640) was obtained.

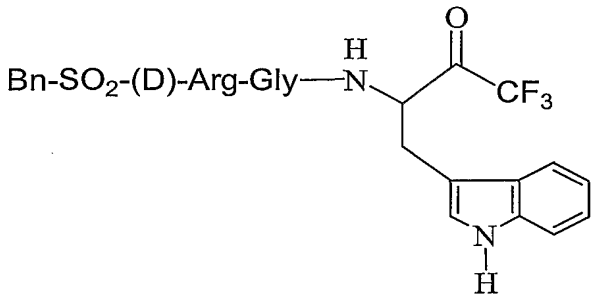
The following scheme illustrates the synthetic reaction scheme leading to the formation of the $-CF_3$ analog:



1) 4 N HCl / Dioxane

2) Bn-SO_2-(D)-Arg(Tos)-Gly-OH, BOP / DIEA / DMF

3) HF



Compositions and Formulations

The compounds of this invention may be isolated as the free acids or bases are converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful in the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of the structures disclosed above may be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt; one salt form of the product may also be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension formulations. In the management of thrombotic disorders, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) may be administered dosages of the compounds that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable

carriers or diluents for therapeutic use are well known to those of skill in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes, such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. The use of the foregoing excipients, carriers, or stabilizers will often result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also acceptable, such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, wherein the administration involves a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, such as, Silastic, silicone rubber or other commercially available polymers.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Exemplary polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, and polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled with a class of biodegradable polymers useful in achieving controlled release of a drug, such as, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross linked or amphipathic block copolymers of hydrogels. As is known in the art, polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor, which may be done by methods well known in the field of pharmacology. Accordingly, it may be necessary for the therapist to titer the

dosage and modify the route of administration to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications involving the compounds are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily. Other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated may be obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like include binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents such as corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, and flavoring agents. When a dosage form is a capsule, it may also contain, in addition to the above materials, a liquid carrier such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection may be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments and, according to generally accepted medical practice, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention may be utilized *in vivo*, which is common in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention may be characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation may be further characterized by disseminated intravascular coagulopathy, which commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which

results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty; (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks; (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma; (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia; (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis); (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve); and (g) those conditions involved in the fitting of prosthetic devices.

Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, the compounds of this invention may be added to or contacted with any medium containing or suspected of containing factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description, make and utilize the compounds of the present invention and practice the claimed methods. The preferred embodiments of the present invention are not to be construed as limiting in any way the remainder of the disclosure.

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferably have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferably have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferably have an IC_{50} of greater than 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor

Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time-dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma-free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of the selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex is used for determining the percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. et al., Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins

immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

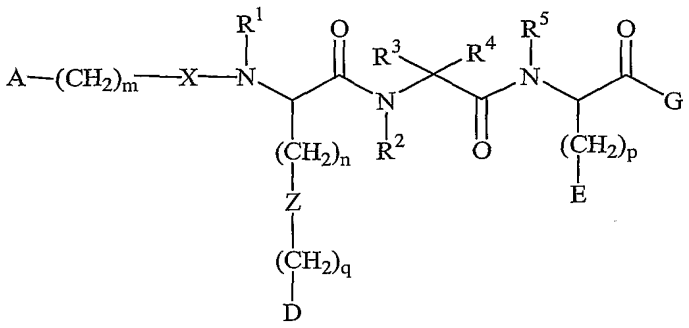
Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at higher doses. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 μg/kg + 2.57 μg/kg/min). Compounds have no significant effect on hematological parameters as compared to saline controls. All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean ± SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description, make and utilize the compounds of the present invention and practice the claimed methods. Other variations upon the above description, particularly the preferred embodiments, will be apparent to one skilled in this field upon reading the above disclosure and the following claims, variations of which are deemed to be within the scope of the present invention. The claims set forth below are utilized to circumscribe the scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

wherein:

R^1 and R^5 are independently H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

R^2 is H, C_{1-6} alkyl, C_{0-4} alkylC_{3-8}cycloalkyl, C_{0-4} alkylaryl, C_{0-4} alkylC_{5-10}heterocycle or together with R^3 or R^4 forms a 5-8 membered ring;

R^3 and R^4 are independently H, C_{1-6} alkyl, C_{0-4} alkylC_{3-8}cycloalkyl, C_{0-4} alkylaryl, C_{0-4} alkylC_{5-10}heterocycle, or R^3 and R^4 together form a 3-8 membered ring;

A is H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, substituted or unsubstituted aryl, or a substituted or unsubstituted 5-10 membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

m is an integer from 0-4;

X is a direct link, -C(=O)-, -SO_2-, -O-C(=O)-, -NR^6-SO_2-, -C(=O)-NR^6-, -S-, -S(O)-, or -NR^6-C(O)-,

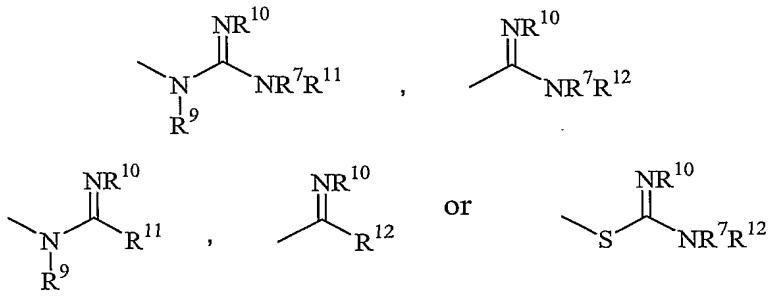
where R^6 is H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

n is an integer from 0-4;

Z is a direct link, C_{1-6} alkylene, C_{3-8} cycloalkylene, divalent aryl, a substituted or unsubstituted divalent 5-10 membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, -S-, -S(O)-, $-SO_2-$, -O-, -C(O)-O-, -C(O)-, -O-C(O)-, $-NR^6-SO_2-$, $-SO_2-NR^6-$, $-C(O)-NR^6-$, or $-NR^6-C(O)-$, where R^6 is H, C_{1-6} alkyl, or C_{1-4} alkylaryl;

q is an integer from 0-2;

D is H, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{5-10} heterocycloalkyl, aryl, C_{5-10} heteroaryl, NR^7R^8,



where R^7, R^8, R^9, R^{10} are independently H, -OH, $-C_{1-6}$ alkyl, aryl, or C_{1-4} alkylaryl;

R^{11} is H, C_{1-6} alkyl, aryl, C_{1-4} alkylaryl, or together with R^9 or R^{10} forms a 5-6 membered ring; and

R^{12} is H, C_{1-6} alkyl, aryl, C_{1-4} alkylaryl, or together with R^{10} forms a 5-6 membered ring;

or alternatively, R^7 and R^{12}, together with the nitrogen atom to which they are attached, can collectively form a 5-10 membered aromatic or nonaromatic heterocyclic ring system containing an additional 0-3 heteroatoms selected from the group consisting of N, O, S, -S(O)- and $-SO_2-$, wherein the aromatic or nonaromatic heterocyclic ring system may be substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, nitro, NH_2, $-NH-C_{1-6}$ alkyl, $-N-(C_{1-6}\text{ alkyl})_2$, $-C_{1-6}$ alkyl, -SH, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{0-4}$ alkylC_{3-8}cycloalkyl, $-C_{0-4}$ alkylaryl and C_{0-4} alkylC_{5-10}heterocycle;

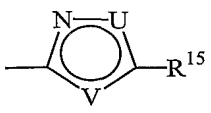
p is an integer from 0-4;

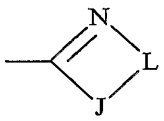
E is:

(a) a cycloalkyl, aryl and C_{0-6} alkylaryl, wherein each of the cycloalkyl, or aryl portions may be unsubstituted or substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and C_{0-4} alkylC_{5-10}heterocycle; or

(b) a substituted or unsubstituted five to ten membered aromatic or nonaromatic heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, wherein the aromatic or nonaromatic heterocyclic ring system can be substituted by 1-4 substituents selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and C_{0-4} alkylC_{5-10}heterocycle;

G is H, -C(O)OR^{13}, -C(O)N$R^{13}R^{14}$, -CF_3, -CF_2CF_3 or a group having the formula:



or


wherein:

R^{13} and R^{14} are independently H, C_{1-6} alkyl, aryl or C_{1-4} alkylaryl;

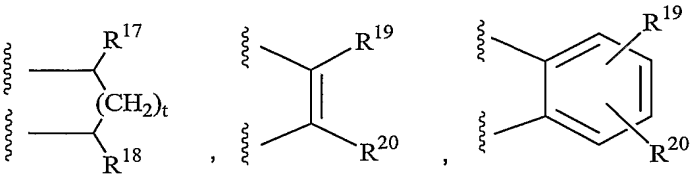
U is -O-, -S-, -N- or -NH-;

V is -O-, -S-, -N- or -NH-, with the proviso that at least one of U or V is -N- or -NH-;

R^{15} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{0-6} alkylaryl, C_{2-6} alkenylaryl, C_{0-6} alkylheterocycle,
C_{2-6} alkenylheterocycle, $-CF_3$ or $-CF_2CF_3$;

J is -S-, -S(O)-, $-SO_2$-, -O-, or $-NR^{16}$, where R^{16} is H, C_{1-6} alkyl or benzyl; and

L is:



a C_6-C_{10} aromatic or nonaromatic heterocyclic ring system substituted by R^{19} and R^{20} and containing 1-4 heteroatoms selected from N, S, and O;

t is an integer from 0-2;

R^{17} and R^{18} are independently H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, $-COOR^{21}$, $-C(O)NR^{21}R^{22}$,
-CN or $-CF_3$; and

R^{19} and R^{20} are independently H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen,
$-NO_2$, $-NR^{21}R^{22}$,$-NR^{21}C(O)R^{22}$, $-OR^{21}$, $-OC(O)R^{21}$, $-C(O)OR^{21}$, $-C(O)NR^{21}R^{22}$,
-CN , $-CF_3$,
$-SO_2NR^{21}R^{22}$ or C_{1-6}alkyl-OR^{21}; and

R^{21} and R^{22} are independently H, C_{1-6}alkyl, aryl, or C_{1-3}alkylaryl,

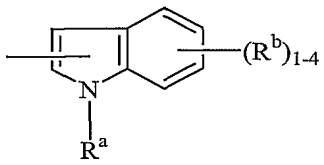
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. The compound of claim 1, wherein
m is an integer from 0-2;
n is an integer from 1-3;
q is an integer from 0-1; and
p is an integer from 1-3.

3. The compound of claim 1, wherein E is a substituted or unsubstituted heterocyclic ring system, wherein the heterocyclic ring system is a member selected from the group consisting of:

acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

4. The compound of claim 1 wherein E is the heterocyclic ring system having the formula:

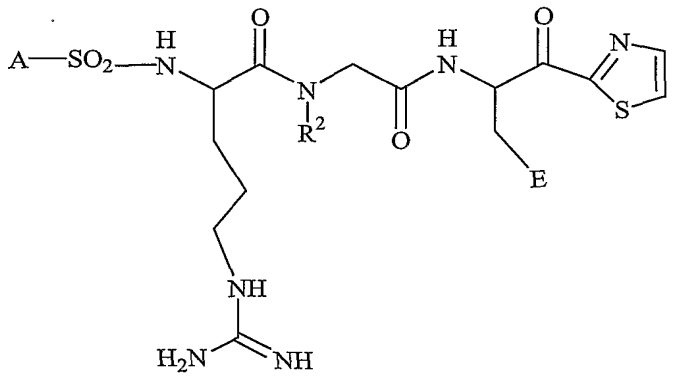


wherein

R^a is a member selected from the group consisting of H, trihaloalkyl, -O, -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and -C_{0-4} alkylC_{5-10}heterocycle;

each R^b is independently a member selected from the group consisting of H, halogen, trihaloalkyl, -OH, -SH, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, nitro, NH_2, -NH-C_{1-6} alkyl, -N-(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -SH, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{0-4} alkylC_{3-8}cycloalkyl, -C_{0-4} alkylaryl and -C_{0-4} alkylC_{5-10}heterocycle.

5. The compound of claim 1, wherein said compound has general formula (Ia):



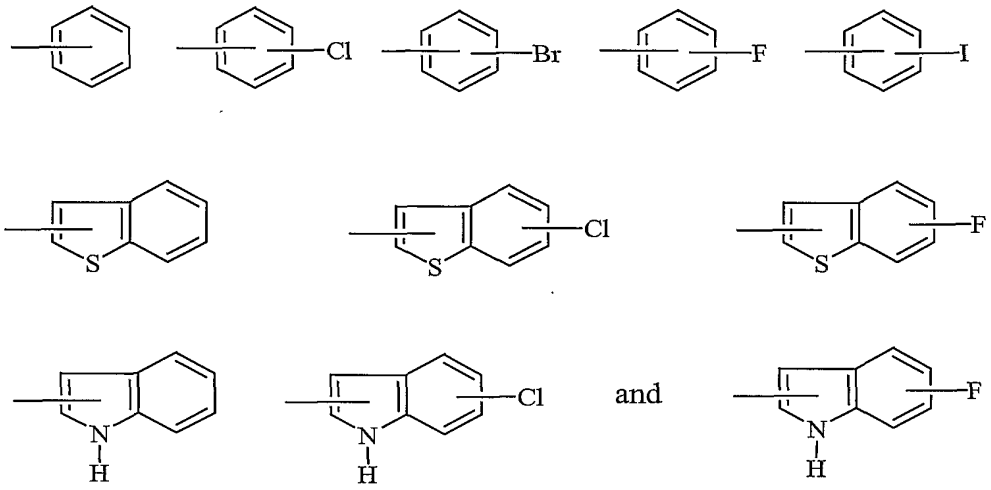
(Ia)

wherein:

A is a member selected from the group consisting of -CH_3, -CH_2-CH_3, -phenyl, and -CH_2-phenyl;

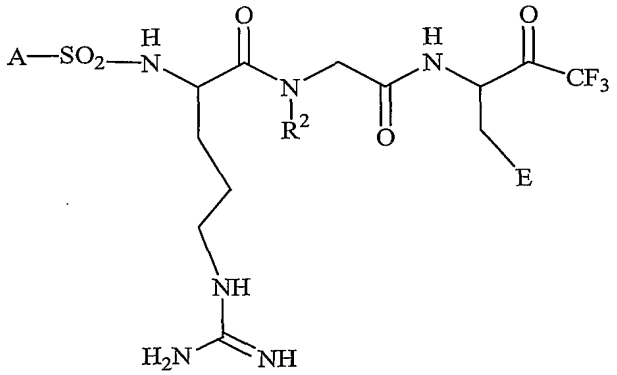
R^2 is a member selected from the group consisting of H, $-CH_3$, and -phenyl; and

E is a member selected from the group consisting of:



and

6. The compound of claim 1, wherein said compound has general formula (Ib):



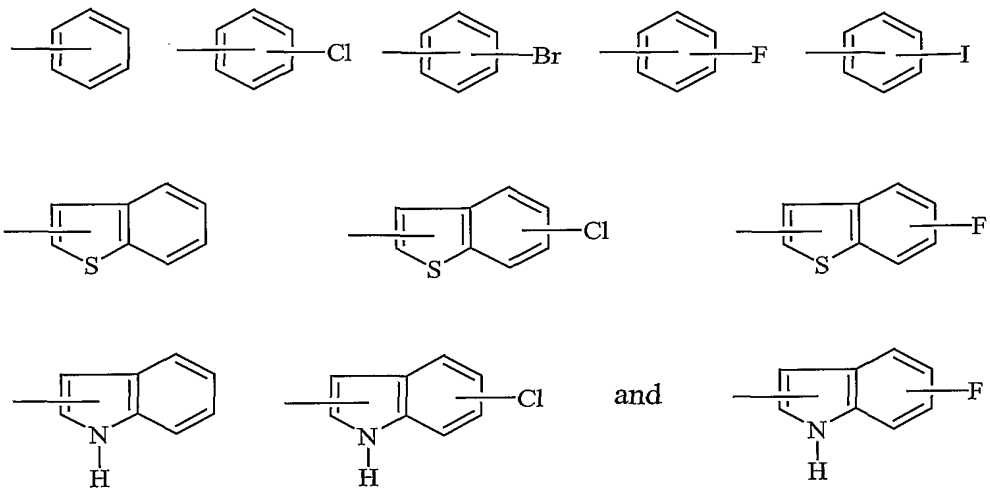
(Ib)

wherein:

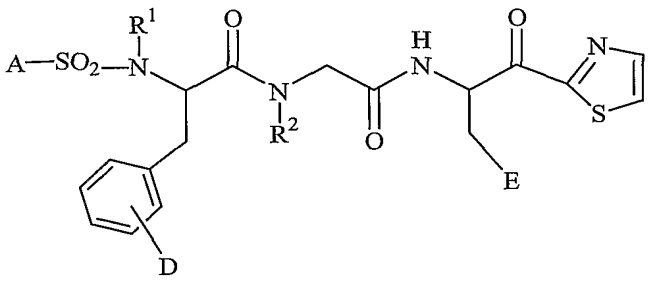
A is a member selected from the group consisting of $-CH_3$, $-CH_2-CH_3$, -phenyl, and $-CH_2$-phenyl;

R^2 is a member selected from the group consisting of H, $-CH_3$, and -phenyl; and

E is a member selected from the group consisting of:



7. The compound of claim 1, wherein said compound has general formula (Ic):



(Ic)

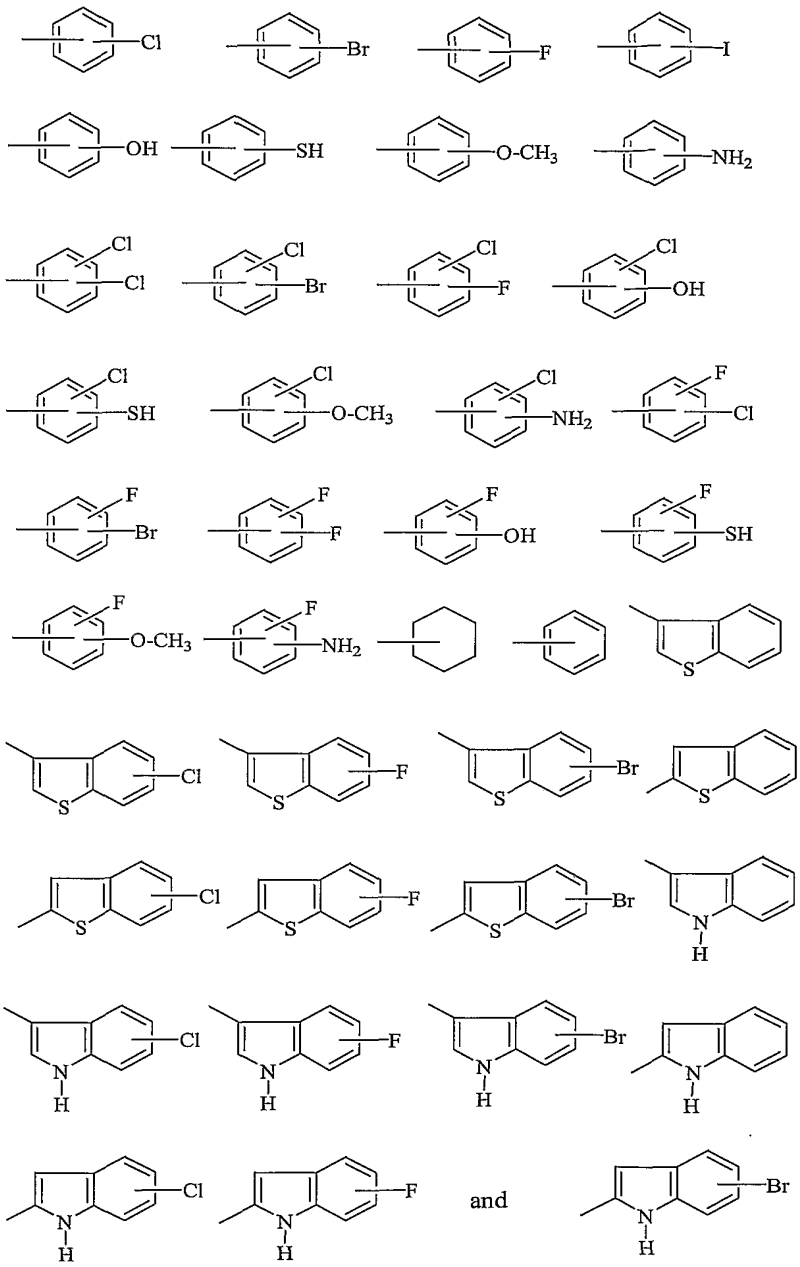
wherein:

A is a member selected from the group consisting of $-CH_3$, $-CH_2-CH_3$ and $-CH_2$-phenyl;

R^1 is a member selected from the group consisting of H, $-CH_3$, and $-CH_2$-phenyl;

R^2 is a member selected from the group consisting of H, -CH_3, and -phenyl;

E is a member selected from the group consisting of:



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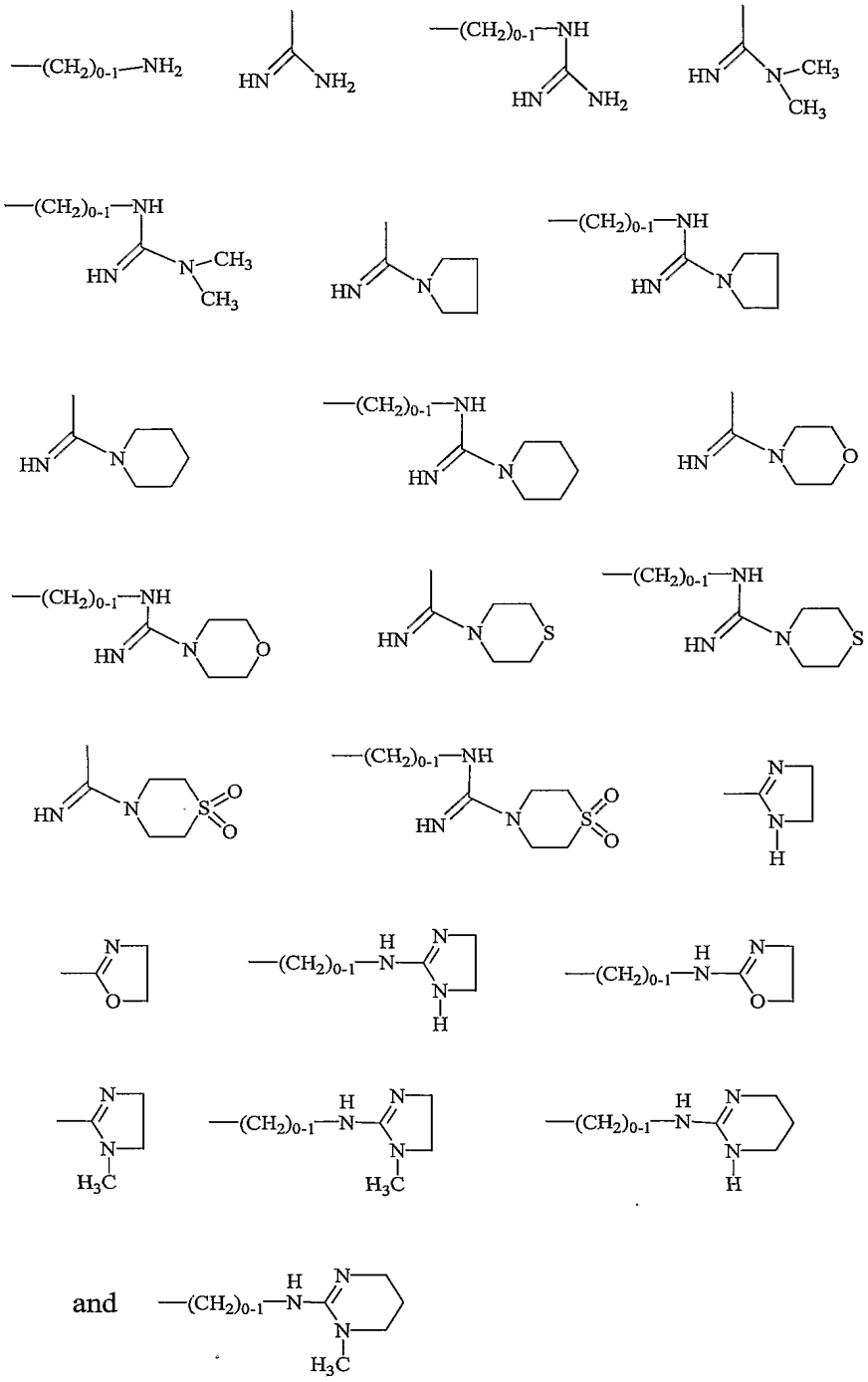
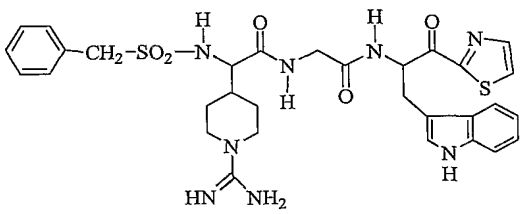
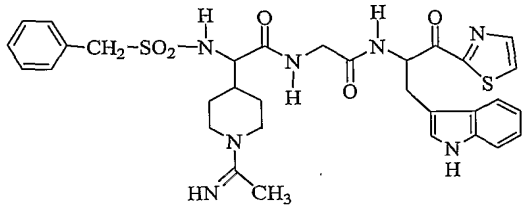
and D is a member selected from the group consisting of:

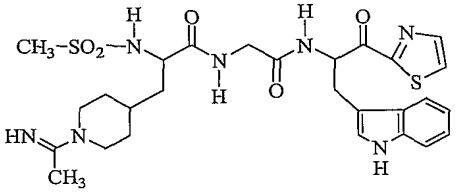


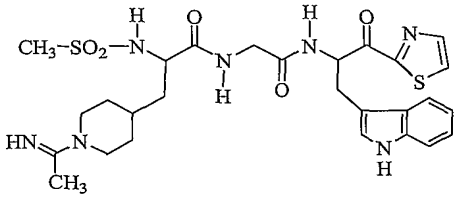
and

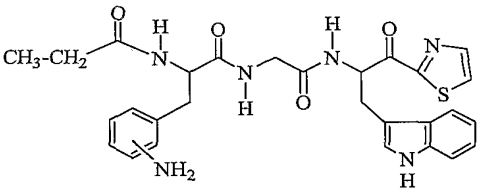
8. The compound of claim 1, wherein said compound is a member selected from the group consisting of:

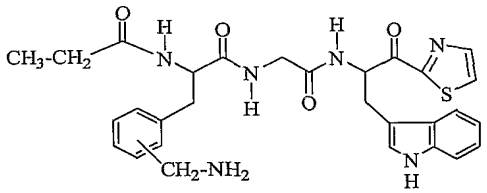


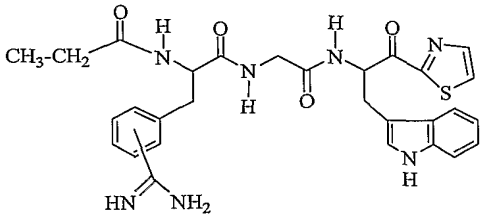


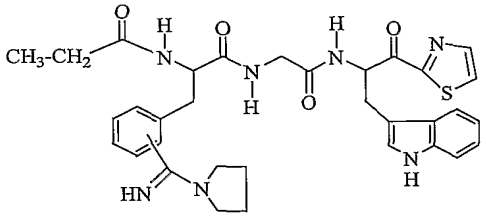


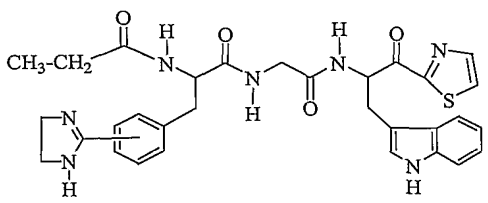


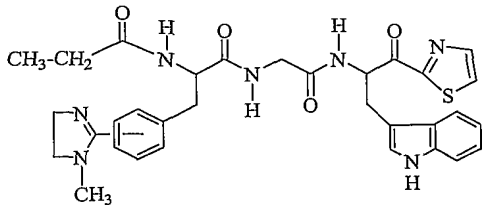


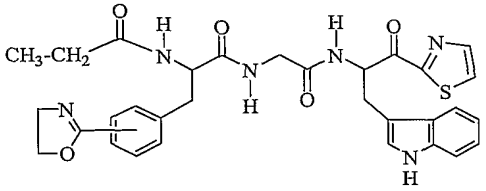


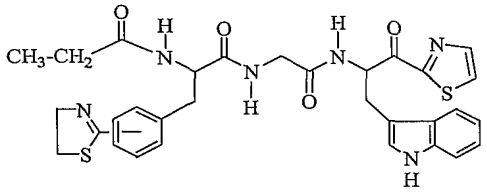


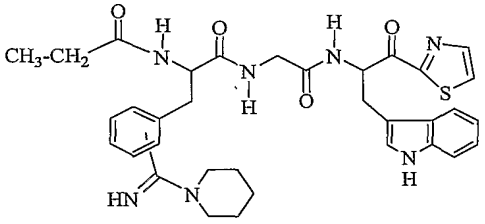


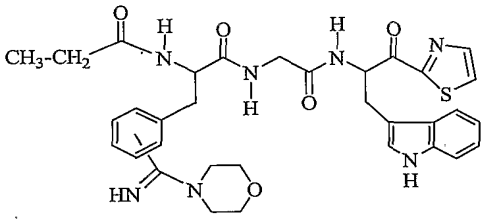


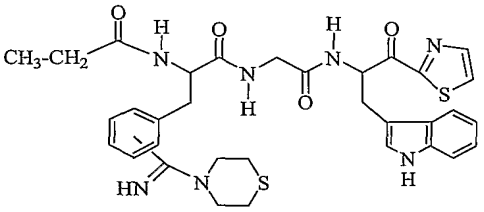


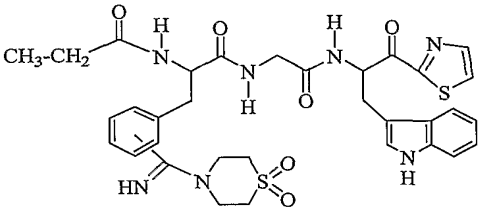




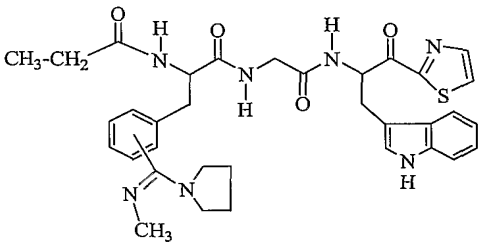








and



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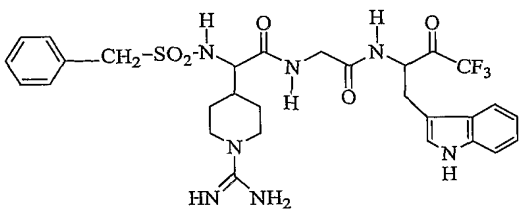
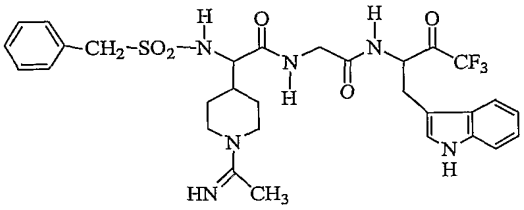
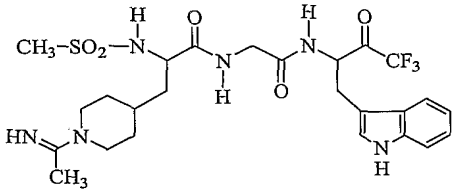
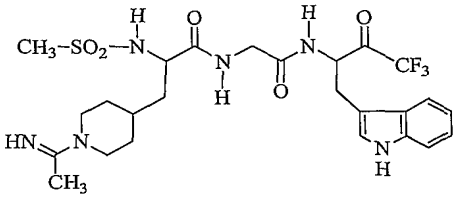
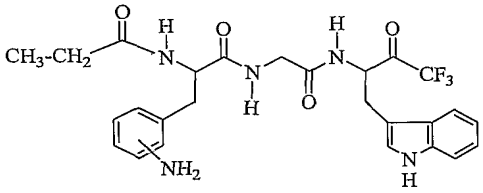
9. The compound of claim 1, wherein said compound is a member selected from the group consisting of:

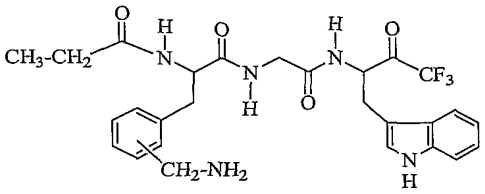


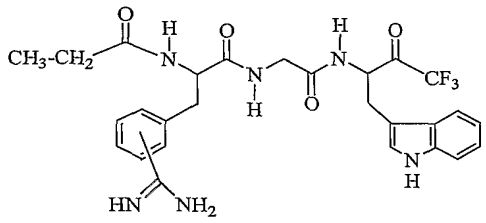


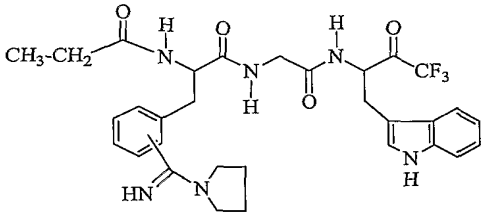












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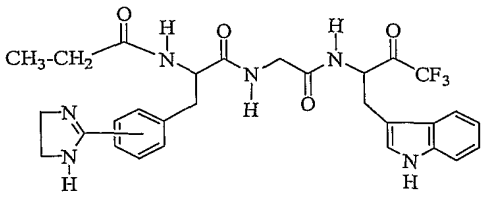
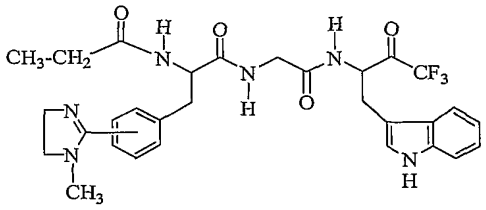
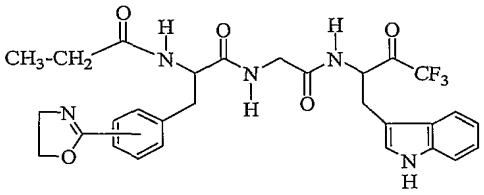
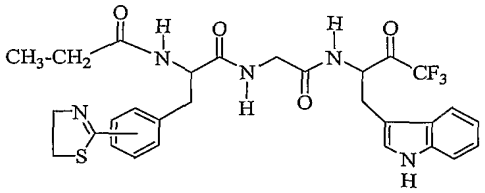
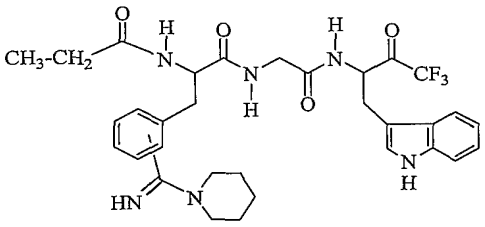
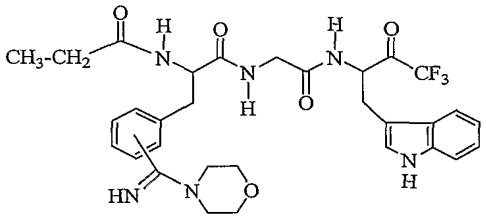


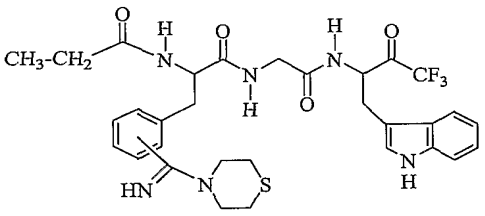


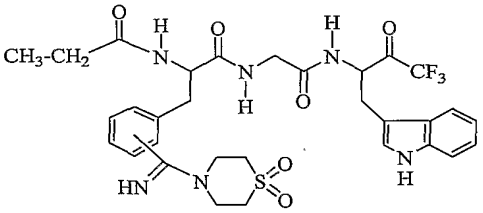




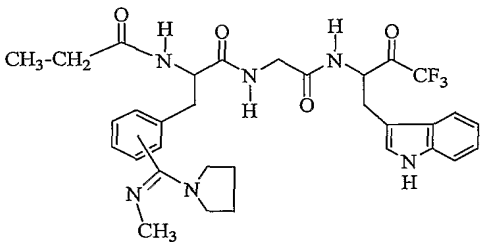








and



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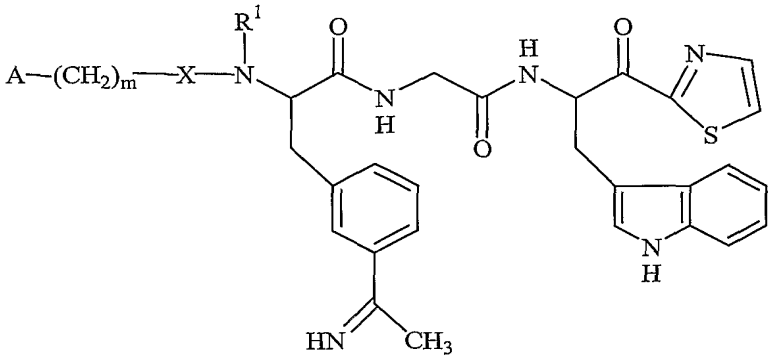
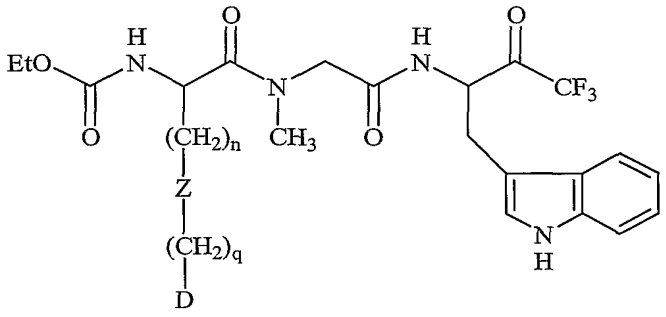
10. The compound of claim 1, wherein said compound has general formula (II):



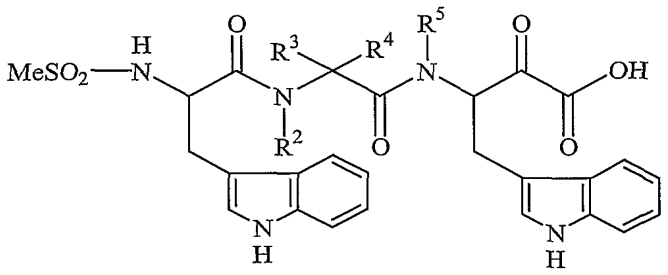
(II)

11. The compound of claim 1, wherein said compound has general formula (III):



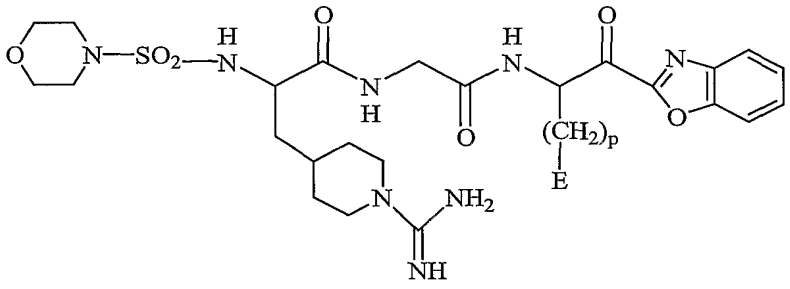
(III)

12. The compound of claim 1, wherein said compound has general formula (IV):



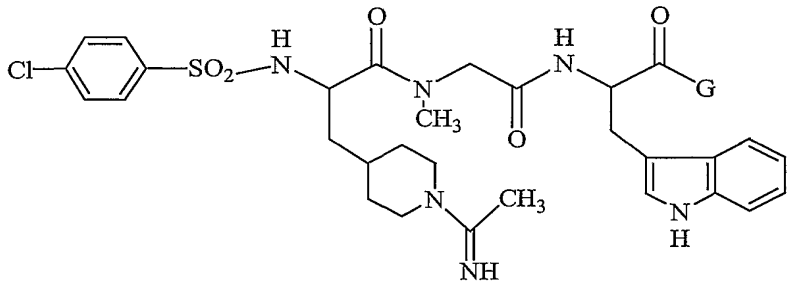
(IV)

13. The compound of claim 1, wherein said compound has general formula (V):



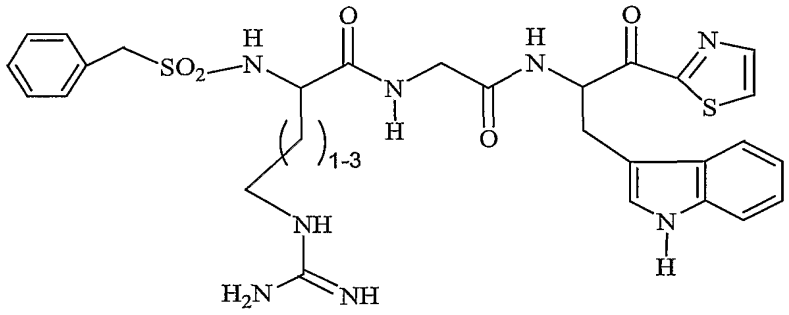
(V)

14. The compound of claim 1, wherein said compound has general formula (VI):



(VI)

15. The compound of claim 1, wherein said compound has general formula (VII):



(VII)

16. A pharmaceutical composition for preventing or treating thrombosis in a mammal comprising

a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and

a pharmaceutically acceptable carrier.

17. A method for preventing or treating thrombosis in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

18. The method of claim 17, wherein said mammal is a human.

19. The method of claim 17, wherein said mammal is prone to or suffers from a cardiovascular disease.

20. The method of claim 19, wherein said cardiovascular disease is at least one selected from the group consisting of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation, septic shock, deep venous thrombosis, pulmonary embolism, reocclusion or restenosis of reperfused coronary arteries, peripheral arterial occlusion, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, and thrombus formation in the venous vasculature and disseminated intravascular coagulopathy.

21. A method for inhibiting coagulation in biological samples comprising the step of administering an anticoagulative effective amount of a compound of claim 1.